REMARKS

This Amendment is in response to the Examiner's Office Action mailed on November 26, 2003 and Applicants' telephone interview with Examiner Dr. Chih-Min Kam and Supervisor Christopher S. F. Low on December 17, 2003. Claims 29 and 31-38 are withdrawn. Claims 2, 3, 5-8, 15 and 39-45 are cancelled. Claims 1, 4, 9-12, 18, 19, 23, 24 and 28 are currently amended. Claims 1, 4, 9-14, 16-28, and 30 are now pending.

Reconsideration is respectfully requested in view of the above amendments to the claims and the following remarks.

I. Claim Objection

The Examiner objected to claim 28 because according to the Examiner, this "claim has not shown the phrase 'anti-neoplastic agent selected from the group consisting of' being deleted." *See* Office Action, at page 2. Applicant have reinstated claim 28 as originally filed. Claim 28 depends on claim 1, which Applicants have currently amended and is in an allowable state. Upon finding that claim 1 is allowable, claim 28 and its dependent claims 29-38 should also be allowable. Therefore, withdrawal of the above objection is respectfully requested.

II. Claim Rejection-35 U.S.C. § 112, First Paragraph

The Examiner rejected claims l, 4, 9-14, 16-28 and 30 under 35 U.S.C. 112, first paragraph, because, according to the Examiner, "***while being enabling for a method of treating a specific cancer*** such as breast, lung, stomach or thyroid cancer, [the specification] does not reasonably provide enablement for a method of treating all cancers." (Office Action of November 26, 2003, at 3) (emphasis added).

Applicants express appreciation to the Examiners for conducting a telephone interview on December 17, 2003. During the interview, Applicants, Examiner Kam, and Supervisor Low discussed the issue of enablement of the claimed method for treating cancer. Examiner Kam and Supervisor Low agreed that treatment of cancer as a "genus" would be enabled if Applicants can show that a group of representative cancer species is associated with aberrant DNA methylation.

Following the Examiner's advice, Applicants submit herewith in the form of IDS numerous references showing that DNA methylation is associated with cancer. For the Examiner's convenience and reference, Applicants list the types of cancer described in the following exemplary publications:

(1) Esteller, M., A Gene Hypermethylation Profile of Human Cancer, *Cancer Research*, (2001) 61:3225, 3229 (associating colon cancer, stomach cancer, pancreatic cancer, liver cancer, kidney cancer, lung cancer, head and neck cancer, breast cancer, ovarian cancer, endometrium cancer, bladder cancer, brain cancer, leukemia, and lymphomas with DNA hypermethylation);

(2) Santini, V., *et al.,* Changes in DNA Methylation in Neoplasia: Pathophysiology and Therapeutic Implications, *Annals of Internal Medicine,* (2001) 134:573-586 (associating colon cancer, breast cancer, gastric cancer, endometrial cancer, retinoblastoma, renal-cell cancer, ovarian cancer, lung cancer, melonoma, mesothelioma, acute myelogenous leukemia, myelodysplastic syndromes, chronic meylogenous leukemia, acute lymphocytic leukemia, chronic lymphocytic leukemia, multiple myeloma, lymphoma, prostate cancer, chronic meylogenous leukemia, prostate cancer, esophageal cancer, acute leukemia, malignant hematologic disease, glioblastoma multiforme with DNA hypermethylation);

(3) Baylin, S.B., *et al.*, *Alterations in DNA Methylation: A fundamental Aspect of Neoplasia*, *Cancer Res.*, (1998) 72: 141-196 (associating retinoblastoma, renal carcinoma, solid tumors, lymphomas, primary acute leukemias, Burkitt lymphoma, bladder cancer, breast cancer, colon cancer, liver cancer, lung cancer, leukemia, brain cancer, renal cancer, prostate cancer, and carcinomas with DNA hypermethylation);

(4) Wajed, S. A., DNA Methylation: An Alternative Pathway to Cancer, *Annals of Surgery,* (2001) Vol. 234, No. 1, 10-20 (associating esophagus, gastric, colorectal, pancreas, lung, bladder, ovary, breast melanoma, leukemia, gastric,

endometrium, ovary, thyroid, kidney, brain, colon, prostate with DNA hypermethylation);

(5) Esteller, M., Epigenetic Lesions Causing Genetic Lesions in human Cancer: Promoter Hypermethylation of DNA Repair Genes, *European Journal of Cancer*, (2000) 3:2294-2300 associating brain cancer, head and neck cancer, lymphomas, lung cancer, breast cancer, kidney cancer, stomach cancer, colon cancer, liver cancer, cancer of the uterus, and prostate cancer to DNA hypermethylation); and

(6) Esteller, M., CpG Island Hypermethylation And Tumor Suppressor Genes: A Booming Present, A Brighter Future, *Oncogene*, (2002) 21:5427-5440 (associating hemangioblastoma, retinoblastoma, glioma, stomach cancer, leukemia, lymphoma, etc. with DNA hypermethylation).

These references show that one of ordinary skill in the art would understand the relationship between DNA hypermethylation and cancer. In view of Applicants' teaching, the claimed method for treating cancer using a combination of a DNA methylation inhibitor and a HDAC inhibitor is enabled. As such, Applicants respectfully request that the Examiner withdraw the rejection under 35 U.S.C. §112, First Paragraph.

IV. Claim Rejection-35 U.S.C. § 112, Second Paragraph

The Examiner rejected claims 1, 4, 9-14, 16-28 and 30 under 35 U.S.C. 112, second paragraph, as being indefinite for failing include an "essential step" – the outcome of the treatment.

Applicants maintain their position that treatment outcome is not a critical step of the present invention, but rather is an inherent feature of this claim. However, in order to expedite prosecution, Applicants have amended independent claim 1 by adding the following limitation: "wherein the combination therapy ameliorates the cancer in the patient." This limitation clarifies that by administering a combination therapy of either decitabine or 5-azacytidine with a histone deacetylase inhibitor selected from the group consisting of hydroxamic acid, cyclic peptide, benzamide, butyrate and depudecin, the outcome is an amelioration of the cancer by improving the condition of the patient.

Based on the claims as amended and the above remarks, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §112, Second Paragraph.

CONCLUSION

Applicants believe that they are entitled to a letters patent and respectfully solicit the Examiner to expedite prosecution of this patent to issuance. Should the Examiner have any questions, the Examiner is encouraged to telephone the undersigned.

Respectfully submitted,

Date: 2/25/04 By: _____

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